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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,229	10/13/2004	Yoram Reiter	28429	6861

7590 06/18/2008

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
06/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,229	REITER ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *141-160 and 197-212* is/are pending in the application.

4a) Of the above claim(s) *150 and 200-211* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *141-149,151-160,197,198 and 212* is/are rejected.

7)☒ Claim(s) *199* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 141-160 and 197-212 are pending in the application.

2. In the prior action, the Final action mailed on October 9, 2007, claims 141-160 and 196-211 were pending; with claims 150 and 200-211 withdrawn from consideration; and claims 141-149, 151-160, and 195-199 under consideration and rejected.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 9, 2008 has been entered.

In the Response of April 2008, the Applicant amended claims 141, 142, 150, 197-211; cancelled claim 196; and added new claim 212.

3. Claims 141-149, 151-160, 197-199, and 212 are under consideration.

Claim Rejections - 35 USC § 112

4. **(Prior Rejection- Withdrawn)** Claims 197 and 198 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for depending from cancelled claim 161. In view of the amendments to the claims, the rejection is withdrawn.

5. **(Prior Rejection- Withdrawn)** Claims 141 and 144-160 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using antibodies to kill or damage cells using the indicated antibodies where the antibody or fragment thereof is attached to a toxin, does not reasonably provide enablement for methods of killing or damaging cells merely through the exposure of the cells to the antibodies. In view of the amendments to the claims, and the arguments in traversal, the rejection is withdrawn.

2. **(Prior Rejection- Withdrawn)** Claim 199 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement with respect to a genus of methods comprising the use of an antibody or fragment thereof that binds to a human antigen-presenting molecule/antigen complex wherein the fragment comprises the sequence of SEQ ID NO: 23. In view of the amendment to the claim, the rejection is withdrawn.

6. **(Prior Rejection- Withdrawn)** Claims 14-149, 151-160, and 196-198 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In view of the amendments to the claims, and the arguments in traversal, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. **(New Rejection)** Claims 141-149, 151-155, 158, 159, and 212 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reiter (PNAS 94:4631-36- of record in the September 2005 IDS), further in view of the teachings of Andersen et al., (WO 97/02342- of record in the action mailed January 2007) and of Chames et al. (PNAS 97:7969-74- of record in the September 2005 IDS). Claims 141-144, 146-148, 151-153, 155, 158, and 159 are drawn to methods for killing cells comprising exposing the cells to an antibody or binding fragment thereof that binds to a complex of an MHC molecule and an antigen from a pathogen, wherein the antibody or fragment is attached to a toxin (esp. Pseudomonas exotoxin A or a portion thereof).

The teachings of Reiter and Andersen were previously described in the action mailed on January 24, 2007. Like Reiter, Chames also indicates that antibodies against HLA-A2 molecule/antigen complexes may be used in therapeutic applications. See e.g., abstract. In addition to these teachings, Chames also indicates that antibodies such as those of Reiter that target HLA-A2 molecule/antigen complexes can be derived from large non-immune phage Fab libraries. See e.g., abstract, and page 7970 (left column).

It is noted that this rejection is similar to that previously applied in the action of January 2007 based on the teachings of Reiter and Andersen. The Applicant traversed that rejection on two grounds. First, the Applicant noted that the teachings of Reiter and Andersen are directed to antibodies that bind mouse MHC-peptide complexes, whereas the present claims are directed against antibodies that bind human versions of such complexes. This argument is not found persuasive. While the teachings of these references refer to examples of antibodies targeting mouse complexes, the references suggest the application of such methods to the treatment of

human disorders. See e.g., Reiter, page 4635, right column; and Andersen, page 5 (referring to the use of human phage libraries for the identification of antibodies with the desired activities). Moreover, Chames specifically teaches the use of such libraries for the identification of human antibodies with such binding properties. See e.g., abstract. Thus, the fact that the Reiter and Andersen references actually disclose anti-mouse MHC complex antibodies fails to overcome this rejection based on what would have been obvious to those of ordinary skill in the art based on the teachings of the cited references.

The Applicant further traversed the rejection based on the teachings of the Declarations by Professors Cerundolo and De Lisi. In each case, the declarations assert that the teachings of the present application have met a long felt need in the art for the generation of TCR-like antibodies. The declarations indicate that there has been failure in the art, and that the teachings of the present application met this need. The arguments were previously found persuasive in overcoming the rejection. However, upon further consideration, the rejections are restated as above and maintained.

It is first noted that in each of the declarations, support for the failure of others relies in part on methods in the prior art wherein the methods rely on screening for antibodies from mice that have been immunized with such antibodies. However, Chames teaches a new method for the identification of such antibodies involving the use of a large non-immunized phage library. It is noted that the use of such a library is the same method disclosed by the present application. See e.g., pages 71 of the application. In particular, it is noted that both Chames and the present application refer to the teachings of the same prior art reference to indicate the phage library to be used. See, Application, page 71 line 5 (referring to the teachings of De Haard, JBC

274:18218-30), and Chames, page 7970 (section entitled "Selection of Phage-Antibodies on Biotinylated complexes"- referring to the same reference). Moreover, it is nowhere specifies how the present application overcomes the asserted deficiencies of the prior art.

It is noted that each of the declarations also assert deficiencies in the teachings of Chames. In specific, the declarations assert that the reference failed to identify antibodies with TCR-like activity that can be used in therapy because the reference could not find conditions where the identified antibodies could be eluted without also dissociating β2m. This argument is not found persuasive. First, the reference teaches that this problem may be overcome through the use of a histidine tag on the antibody. See, Chames, page 7972. Second, it is not clear how this is relevant as there would be no need for the elution of the antibodies from complexes when the antibodies are being applied for therapeutic use. The context of the failure indicated in the reference is in the characterization of the Fab in a binding-experiment. However, there would be no need for such an elution in a therapeutic context.

Second, the declarations indicate that the reference teaches on page 7972 that the Fab purified in the reference failed to detect HAL-A1 cells incubated with the target peptide antigen. However, the reference itself indicates that this was not unexpected due to its low binding affinity. However, the reference also indicates that the low binding affinity was not expected due to the size of the phage library, indicating that those of ordinary skill in the art would expect antibodies targeting other complexes may be more common. Further, it would have been obvious to those of ordinary skill in the art to perform additional screening for antibodies with higher affinity. This is particularly the case as the Chames reference concludes that TCR-like antibodies can be selected through the use of such libraries for use in immunotherapeutic methods.

In view of the specific suggestions in the art that antibodies with the binding characteristics identified in the claims be used for the immunotherapeutic methods claimed, and as Chames specifically teaches the use of the same type of library and similar methodology to that disclosed in the present application for the identification of such antibodies and indicates that such methodology would be useful for the identification of antibodies useful in immunotherapeutic methods, the assertions that the present application has met a previously unmet need is not found persuasive. The teachings of Chames appear to teach a method that overcomes the problems faced in the prior art by providing a method for the identification of antibodies that may be used in such methods. Thus, it is not clear that the long felt need remained unresolved after the teachings of Chames which specifically indicates that the desired antibodies can be obtained through a method similar to that of the present application. The arguments presented asserting that the present application has overcome the obviousness rejection on the bases of resolving a long-felt need in the art is therefore not found persuasive.

The rejection as restated is therefore maintained.

5. **(New Rejection)** Claims 141-149, 151-159, and 212 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reiter in view of Andersen and Chames as applied above, further in view of the teachings of Matsushita et al. (U.S. 5,591,829- of record in the September 2005 IDS). This rejection, without the teachings of Chames, was made in the action of January 2007. The additional teachings of Chames are described above. As no additional arguments were made with respect to this rejection over those asserted to the rejection over Reiter in view of Andersen, the rejection is maintained over such arguments for the reasons indicated above.

6. **(New Rejection)** Claims 141-149, 151-160, and 212 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reiter in view of Andersen and Chames as applied above, further in view of the teachings of Saito et al. (J Virol 75: 1065-71- of record in the September 2005 IDS). This rejection, without the teachings of Chames, was made in the action of January 2007. The additional teachings of Chames are described above. As no additional arguments were made with respect to this rejection over those asserted to the rejection over Reiter in view of Andersen, the rejection is maintained over such arguments for the reasons indicated above.

7. **(New Rejection)** Claims 141-149, 151-155, 158, 159, 197, 198, and 212 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reiter in view of Andersen and Chames as applied above, further in view of Carter et al. (U.S. 6,054,297). Additional claims 197 and 198 are directed to embodiments wherein the constant region of the antibody is capable of inducing antibody-dependent cell mediated toxicity, or of initiating a complement cascade. The teachings of the previously cited references have been described above. While the references suggest the use of such antibodies in immunotherapeutic methods, including against viral infections, the references do not specifically teach or suggest the use of constant domains such as described in claims 197 and 198. However, Carter indicates that the use of such constant regions was known in the art. See e.g., columns 2, 24, and 44-45. It would therefore have been obvious to those of ordinary skill in the art to have used such constant domains in the immunotherapeutic antibodies suggested by the cited art.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. **(Prior Rejection- Withdrawn)** Claims 141-160 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-50 of copending Application No. 11/203,137, or the copending claims in view of the teachings of

Reiter and Andersen in view of any of Hoogenboom, Matsushita, or Saito as applied above. As the copending claims are withdrawn from examination, the rejection is withdrawn.

9. **(Prior Rejection- Restated)** Claims 141-149, 151-160, 197, and 198 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8, 11, and 13 of copending Application No. 11/629194, or the copending claims in view of the teachings of Reiter, Chames, and Andersen and any of Matsushita, Saito, or Carter as described above. It is noted that, while the present claims have been amended, the copending claims also render obvious methods of using a specific antibody, which was identified with a method such as the one used in the present application, and which would therefore be expected to have the same or similar binding characteristics. As it is not Office policy to hold the rejection in abeyance, the rejection is maintained.

Conclusion

10. No claims are allowed. Claim 199 is objected to for depending on a rejected claim.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is (571)272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Z. Lucas/
Patent Examiner, AU 1648